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Febuxostat: a safe and effective therapy for hyperuricemia and gout

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Febuxostat is a novel, nonpurine, selective xanthine oxidase inhibitor and is a potential alternative to allopurinol for patients with hyperuricemia and gout. Unlike allopurinol, which undergoes renal elimination, febuxostat is metabolized via hepatic conjugation and oxidation. Phase III studies have shown that febuxostat, at a once-daily dose of 80, 120 or 240 mg (safety dose), is more effective than allopurinol (300 mg) in reducing and maintaining serum urate concentrations lower than 6 mg/dl. Reductions in gout flares and tophus areas with febuxostat treatment are similar to those occurring with allopurinol therapy. Patients with moderate renal impairment can achieve significant serum urate reductions, without dose adjustments. Therefore, febuxostat represents a viable treatment choice, with documented efficacy and safety in hyperuricemia and gout.

Gout is a disease in which tissue deposition of monosodium urate crystals occurs as a result of hyperuricemia, defined as a serum urate concentration that exceeds the limit of solubility (~6.8 mg/dl [400 µmol/l]). Clinical manifestations include recurrent attacks of acute inflammatory arthritis, accumulation of urate crystals in the form of tophaceous deposits and nephropathy. Despite advances in our understanding of the pathogenesis of gout and the availability of allopurinol for approximately 50 years, hyperuricemia and its sequelae are not only prevalent, but the incidence and costs associated with this disorder continue to increase [1].

Epidemiological studies suggest that the overall burden of gout is substantial and growing. The prevalence of gout and clinically significant hyperuricemia is increasing in both sexes over the age of 65 years. Males still carry most of the burden of disease [2]. Lifestyle and dietary factors may explain the increasing incidence of gout [3]. Obesity and weight gain are strong risk factors for gout in men, while weight loss is protective. Hypertension and diuretic use are also important independent risk factors for gout. Higher levels of meat and seafood consumption are associated with an increased risk of gout, whereas a higher consumption of dairy products is associated with a decreased risk [4,5]. Alcohol intake is strongly associated with an increased risk of gout. This risk varies substantially according to type of alcoholic beverage. Beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk [6]. Currently available treatments of hyperuricemia in patients with gout reduce serum urate concentration either by enhancing renal excretion of uric acid (uricosuric

agents) or by decreasing urate synthesis (xanthine oxidase inhibitors). These therapeutic options are not without their limitations.

Market overview

Allopurinol is a competitive inhibitor of xanthine oxidase, preventing the oxidation of xanthine to uric acid. Allopurinol and its active metabolite, oxipurinol, are structural analogs of hypoxanthine and xanthine, respectively [7]. As oxipurinol is excreted primarily by renal mechanisms, its half-life is prolonged in renal failure, necessitating a reduction in allopurinol dosage. The most commonly used dose of allopurinol is 300 mg daily. There is considerable variation in the daily dose required to control serum urate levels, ranging from 100 to 800 mg and more [8]. The most concerning and potentially life-threatening adverse event is allopurinol hypersensitivity syndrome, consisting of an erythematous rash, fever, hepatitis, eosinophilia and renal failure [9,10]. Renal dysfunction appears to be a risk factor in the development of allopurinol hypersensitivity syndrome. Avoidance of allopurinol or use of reduced doses in patients with renal insufficiency may reduce the incidence of allopurinol toxicity [11]. Patients with allopurinol-induced maculopapular eruptions have been successfully managed with slow oral desensitization, temporary withdrawal of the drug and subsequent reintroduction with dosage adjustment [12].

The potential drug interactions between allopurinol and azathioprine or 6-mercaptopurine must be considered. Both drugs are partly metabolized by xanthine oxidase, thus inhibition of this enzyme by allopurinol may increase their immunosuppressant and toxic effects.

Keywords: febuxostat, gout, hyperuricemia, renal safety

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Poor compliance is a drawback of allopurinol therapy. A recent, large, retrospective study of patients with gout who were prescribed allopurinol showed noncompliance with therapy for an average of 44% of their treatment periods over 2 years [13].

A series of 1-phenylpyrazoles have demonstrated xanthine oxidase inhibitory activity. The most potent of these, Y-700, has been evaluated in healthy male volunteers. It decreased serum uric acid in a dose- and time-dependent manner. It is eliminated predominantly via the liver, thus it may be safe in patients with renal failure. However, it remains under investigation at this time [14].

The uricosuric drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate–anion exchanger in the proximal tubule that mediates urate reabsorption [15]. The use of uricosuric agents, such as probenecid or sulfapyrazone, is limited in patients with renal insufficiency. Other limitations of their use are the need for multiple daily doses, potential drug interactions and the risk of nephrolithiasis.

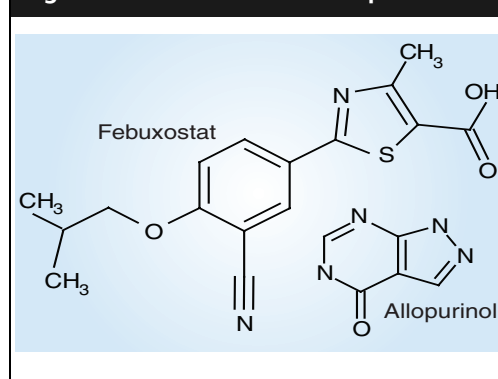
Losartan, an angiotensin II receptor antagonist, has been shown to increase urinary uric acid excretion and hence lower serum uric acid levels [16]. A combination of losartan and fenofibrate reduces serum uric acid concentrations further, with a concomitant increase in uric acid excretion. Fenofibrate alone reduces plasma uric acid concentration; however, the effect is weak when compared with combination therapy [17]. Further studies are required to ascertain the usefulness of combined losartan and fenofibrate in the treatment of hyperuricemia and gout.

Uricase (urate oxidase) is a novel therapy for reduction of serum uric acid levels. Uricase catalyzes the conversion of urate to a more soluble molecule, allantoin. Uricase is present in most mammals, but absent in humans due to a mutational inactivation of uricase genes. Preliminary efficacy and safety data from single infusions of pegylated uricase have been reported [18,19]. The development of antipegylated uricase antibodies has been documented and may limit efficacy in some patients [20]. Further studies are needed to assess the immunogenicity and long-term safety of pegylated uricase in the treatment of hyperuricemia and gout.

Introduction to the compound

Febuxostat is an oral, once daily, selective non-purine xanthine oxidase inhibitor. A comparison of the structure of febuxostat with allopurinol is shown in Figure 1.

Figure 1. Febuxostat and allopurinol.



Chemistry

Febuxostat is a thiazolecarboxylic acid derivative. It is described chemically as 2-[3-cyano-4-(2-methylpropoxy)-phenyl]-4-methylthiazole-5-carboxylic acid. It is also known as TEI-6720 or TMX-67. It does not structurally resemble purines or pyrimidines, unlike allopurinol, which is a purine-based analog [21].

Pharmacodynamics

Febuxostat is a potent xanthine oxidase and xanthine dehydrogenase inhibitor, but has minimal effects on other enzymes involved in purine and pyrimidine metabolism, in contrast to allopurinol [22–25]. It exhibits potent mixed-type inhibition of both the oxidized and reduced forms of xanthine oxidase. This mechanism is mediated by high-affinity binding of febuxostat to the enzyme in a molecular channel leading to the molybdenum–pterin active site. The binding of febuxostat to xanthine oxidase persists, independent of the redox state of the molybdenum cofactor, and blocks substrate access to the active site. The enzyme inhibitor complex is stable and not influenced by changes in the redox status of the cofactor, in contrast to the oxypurinol-inhibited enzyme. This allows for lower therapeutic doses [22,23].

Pharmacokinetics & metabolism

Following its oral administration in healthy human subjects, febuxostat is absorbed rapidly, with a maximum absorption time of approximately 1 h. The drug is highly bound to albumin in blood (~90%) and appears to have a low-to-medium volume of distribution of approximately 0.7 l/kg. Daily febuxostat doses in the range of 10–120 mg resulted in proportional mean serum urate reductions ranging from 25 to 70%, and proportional increases in maximum febuxostat plasma concentrations and the area under plasma concentration versus time curves in healthy

adults. Febuxostat is metabolized mainly in the liver to acyl-glucuronide metabolites and, to a lesser extent, to oxidative metabolites by cytochrome P450 enzymes [26].

Single-dose febuxostat administered to subjects with normal, mild and moderate renal impairment resulted in a less than twofold difference in plasma unchanged febuxostat levels among the impaired renal function groups. This indicates that renal impairment has little impact on the pharmacokinetics and pharmacodynamics of febuxostat [27].

In addition, the serum urate-lowering effect of febuxostat appears unaltered in those with renal compromise [21].

Mild-to-moderate hepatic dysfunction does not significantly change the plasma pharmacokinetic parameters of febuxostat or its active metabolites. Dose adjustment is not required in those with mild-to-moderate degrees of hepatic impairment [28].

Medications frequently coadministered with urate-lowering agents include nonsteroidal anti-inflammatory drugs and colchicine. Indomethacin, naproxen and colchicine have no effect on the pharmacokinetics of febuxostat. Similarly, febuxostat has no effect on the pharmacokinetics of these drugs and, therefore, no dose adjustments are required [29,30].

Clinical efficacy

Pivotal Phase II trial

The safety and efficacy of febuxostat in establishing normal serum urate concentrations in gout patients with hyperuricemia (≥ 8 mg/dl) was assessed in a 28-day, randomized, double-blind, placebo-controlled trial [31]. In total, 153 patients (aged 23–80 years) were included. Subjects received febuxostat (40, 80 or 120 mg) or placebo once daily for 28 days and colchicine prophylaxis for 14 days prior to and 14 days after randomization. The primary end point was the proportion of subjects with serum urate levels lower than 6.0 mg/dl on day 28. This target was attained by 0% of those receiving placebo and in 56, 76 and 94% of those receiving 40, 80 and 120 mg febuxostat, respectively.

Greater proportions of febuxostat- than placebo-treated patients achieved serum urate levels of less than 6 mg/dl at each visit ($p < 0.001$ for each comparison). All dosages of febuxostat resulted in a significant reduction in serum urate concentrations. The incidence of treatment-related adverse events was similar in the febuxostat and placebo groups.

Pivotal Phase III trial

The Febuxostat versus Allopurinol Controlled Trial (FACT), a Phase III, randomized, double-blind trial, compared the safety and efficacy of febuxostat with that of allopurinol in 762 patients with gout and serum urate levels of at least 8 mg/dl [32]. As allopurinol was included in the study, patients with a serum creatinine concentration of more than 1.5 mg/dl or an estimated creatinine clearance of less than 50 ml/min/1.73 m² of body surface area were excluded. Participants were randomly assigned to receive either febuxostat (80 or 120 mg) or allopurinol (300 mg) once daily for 52 weeks. Prophylaxis against gout flares was provided for week 1–8 with either naproxen or colchicine. Patients were assessed and serum urate levels measured at weeks 2 and 4, and monthly thereafter. The primary end point of the study was a serum urate level of less than 6 mg/dl at the last three monthly visits. The secondary end points were the proportion of subjects with serum urate levels of less than 6.0 mg/dl at each visit and the percentage reduction from baseline in the serum urate concentration at each visit. Clinical end points included the reduction from baseline in tophus area, the change in the number of tophi at each visit and the proportion of patients requiring treatment for gout flares from week 9 to 52.

The primary end point was reached by 53% of patients receiving 80 mg of febuxostat, 62% of those receiving 120 mg of febuxostat and 21% of those receiving allopurinol ($p < 0.001$ for the comparison of each febuxostat group vs the allopurinol group). By the first assessment post randomization, the proportion of subjects with serum urate concentrations of less than 6.0 mg/dl was already significantly higher in the groups receiving febuxostat than those receiving allopurinol ($p < 0.001$). These differences were sustained at all visits until completion of the study ($p < 0.001$). The mean percentage reduction from baseline serum urate concentration at the final visit was greater in both febuxostat groups than in the allopurinol group. *Post hoc* analysis showed that, at week 52, the proportion of patients with final serum urate concentrations of less than 5.0 or less than 4.0 mg/dl were significantly greater in both of the febuxostat groups than in the allopurinol group ($p < 0.001$). However, it is probable that allopurinol would have been more effective at lowering urate concentration if the study design had permitted dose titration according to the serum urate level, as occurs routinely in clinical practice.

More patients withdrew from the study in the febuxostat groups than in the allopurinol group, with 88 patients withdrawing from the febuxostat 80 mg group, 98 from the febuxostat 120 mg group and 66 from allopurinol therapy.

The percentage reduction in tophus area was assessed in 156 subjects who had tophi at baseline. By week 52, the median reduction in tophus area was 83% in patients receiving 80 mg of febuxostat and 66% in those receiving 120 mg of febuxostat, as compared with 50% in those receiving allopurinol ($p = 0.08$ for 80 mg of febuxostat vs allopurinol; $p = 0.16$ for 120 mg of febuxostat vs allopurinol). No significant change was noted in the number of tophi over time in any of the treatment groups.

Acute gout flares are an anticipated problem early in the course of urate-lowering therapy. During the initial 8-week prophylaxis period in the FACT study, a significantly greater proportion of subjects receiving 120 mg of febuxostat required treatment for a gout flare than those receiving either 80 mg of febuxostat or allopurinol ($p < 0.001$ for both comparisons). The overall incidence of gout flares between weeks 9 and 52 was similar in all groups, with 64% of patients receiving 80 mg of febuxostat, 70% receiving 120 mg of febuxostat, and 64% receiving allopurinol (Table 1).

The 28-week allopurinol versus febuxostat in severe gout (APEX) study compared febuxostat, allopurinol and placebo in subjects with hyperuricemia and gout [33]. This study uniquely included 40 subjects with moderately impaired

renal function (serum creatinine levels of 1.6–2.0 mg/dl). A total of 1067 subjects with gout and serum urate levels greater than 8.0 mg/dl were randomized to daily placebo, febuxostat 80, 120 or 240 mg, or allopurinol. No dose adjustments were made in the placebo or febuxostat groups based on renal function. Patients receiving allopurinol did have dose adjustments based on renal dysfunction. Patients with baseline serum creatinine of less than 1.5 mg/dl received 300 mg of allopurinol and those with serum creatinine of 1.6–2.0 mg/dl received 100 mg of allopurinol. The primary end point was the proportion of subjects with serum urate levels of less than 6.0 mg/dl at each of the last three assessments.

The primary end point was achieved in 48, 65 and 69% of those in the febuxostat 80, 120 and 240 mg groups, respectively, and 22% of those receiving allopurinol. Subjects with moderate renal impairment achieved serum urate concentrations of less than 6.0 mg/dl at the last three visits in 44% of those receiving 80 mg, 45% of those receiving 120 mg and 60% of those receiving 240 mg febuxostat. In total, 10% of patients with renal impairment receiving allopurinol achieved the primary end point.

Safety & tolerability

Febuxostat appears to be a well tolerated and safe choice of drug for the treatment of gout patients with hyperuricemia, as demonstrated in both Phase II and III studies.

Table 1. Results from a Phase III trial comparing febuxostat with allopurinol.

Outcome measure/study end points	Febuxostat 80 mg/day	Febuxostat 120 mg/day	Allopurinol 300 mg/day
Primary end point			
Serum urate <6.0 mg/dl at last three monthly visits	136/255 (53%)	154/250 (62%)	53/251 (21%)
Secondary end points			
Serum urate levels <6.0 mg/dl at final visit	185/249 (74%)	193/242 (80%)	88/242 (36%)
Incidence of gout flares between weeks 9 and 52	147/228 (64%)	150/215 (70%)	150/234 (64%)
Tophus change from baseline: median percentage change in tophus area	32% (-83)	26% (-66)	30% (-50)
Tophus change from baseline: median change in the number of tophi/patient	33 (0)	28 (-1)	35 (0)

Data taken from [31].

When compared with placebo, febuxostat at doses of 40, 80 and 120 mg did not confer any increased risk of treatment-related adverse events. Gout flares were assessed and found to occur with similar frequency in the placebo and 40 mg febuxostat groups, at rates of 37 and 35%, respectively. Gout attacks occurred at greater frequency at higher doses of febuxostat, 43% in those taking 80 mg and 55% at the 120 mg dosage. During prophylaxis with colchicine, gout attacks occurred less frequently [31].

In the FACT study, most of the adverse events secondary to febuxostat were mild to moderate in severity and included abnormal liver function test results, diarrhea, headaches and musculoskeletal symptoms [32].

Four patients died in the febuxostat groups and none in the allopurinol group. There were two deaths in the group receiving 80 mg of febuxostat, one from congestive cardiac failure and respiratory failure and one from retroperitoneal bleeding ascribed to anticoagulant therapy. Two deaths occurred in the group receiving 120 mg of febuxostat, one from metastatic colon cancer and one from cardiac arrest. All deaths were judged by the investigators to be unrelated to the study drugs [32].

The most common event leading to withdrawal from the study was the development of abnormal liver function tests. This resulted in withdrawal of five subjects receiving 80 mg of febuxostat and seven receiving 120 mg. Eight patients discontinued febuxostat treatment due to skin rashes. Most of these were localized and transient, occurring during prophylactic treatment with either naproxen or colchicine, and were resolved with topical treatment. No serious rashes or hypersensitivity reactions occurred in the study [32].

Treatment-related adverse events are not increased in patients with moderate degrees of renal insufficiency [33]. Febuxostat may be a useful therapeutic option in patients with gout and renal impairment.

Regulatory affairs

Based on results from a Phase III clinical trial, TAP Pharmaceutical Products Inc. (IL, USA), the manufacturers of febuxostat, have submitted an application seeking US FDA approval for febuxostat in the management of hyperuricemia in patients with chronic gout.

Conclusion

Febuxostat has a proven efficacy in significantly reducing and maintaining serum urate concentrations of less than 6 mg/dl in patients with gout. Doses of 80, 120 and 240 mg are effective. Febuxostat has an excellent safety profile that is comparable with placebo. In particular, febuxostat has not been associated with nephrotoxicity and does not require renal function monitoring. For these reasons, febuxostat should be considered when treating patients with hyperuricemia and gout. However, indications for the use of febuxostat will most likely be the same as those for allopurinol. Since the newer febuxostat will most likely cost more than traditional therapies such as allopurinol, the relative cost of febuxostat versus allopurinol is likely to influence the decision to use one agent or the other. Long-term studies are ongoing to provide further evaluation of the safety and efficacy profile of febuxostat.

Future perspective

A significant number of patients with hyperuricemia are poorly responsive to current therapies. Hopefully, new treatment modalities under investigation in ongoing clinical trials will lead to a reduction in this number. In addition, exploration of new therapeutic agents such as specific proinflammatory signal transduction cascades or cytokines could offer new therapeutic options for acute gout. More data are required to guide appropriate treatment strategies for acute gout in specific clinical groups, such as elderly patients or those with renal failure, hypertension or heart disease. Studies are also needed to examine interindividual variation and the influence of genetic and constitutional factors on treatment effects.

Further research into inhibitors of crystal growth in gout could lead to the development of useful drugs. In addition to this, the potential for predisposition to gout should be considered in the screening of new drugs for diseases unrelated to gout. Patient compliance is essential for the effective management of gout and this remains a problem. Therefore, the impact of patient education, information access and patient preference on adherence to management strategies of gout all require further consideration.

Executive summary

Background

- Epidemiological studies show that the incidence and prevalence of gout is increasing.
- Lifestyle and dietary factors play a significant role in the increasing incidence of gout.
- Currently available treatments of hyperuricemia have limitations, particularly in patients with renal impairment. Other issues include poor compliance levels and potential medication interactions.

Pharmacodynamics & pharmacokinetics

- Febuxostat is an oral, once daily, selective nonpurine xanthine oxidase inhibitor.
- It is a thiazolecarboxylic acid derivative, unlike allopurinol, which is a purine-based analog.
- Hepatic conjugation and oxidative metabolism are the major pathways of elimination of febuxostat from the body.
- Renal elimination does not appear to play a significant role.
- Mild-to-moderate hepatic dysfunction does not significantly change the plasma pharmacokinetics of febuxostat or its active metabolites.

Clinical efficacy

- Febuxostat, at a daily dose of 80, 120 or 240 mg (safety dose), is more effective than allopurinol 300 mg in reducing and maintaining serum urate concentrations lower than 6 mg/dl.
- Reductions in tophus area with febuxostat treatment are similar to those with allopurinol therapy.
- The incidence of gout flares is similar for febuxostat and allopurinol therapy.
- Subjects with moderate renal impairment can achieve significant serum urate reductions, without dose adjustment of febuxostat.

Safety & tolerability

- In general, febuxostat is well tolerated, with a safety profile comparable to placebo.
- The most common cause of discontinuation from clinical studies has been abnormal liver function tests.
- Febuxostat is well tolerated in patients with moderate degrees of renal insufficiency and dose adjustment is not required.
- Long-term studies are ongoing to provide further evaluation of the safety profile of febuxostat.

Dosage & administration

- Febuxostat is administered as a once daily, oral dose.
- Doses of 80 and 120 mg have been shown to be efficacious and well tolerated.

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